Heart Rate, Autonomic Function, and Future Changes in Glucose Metabolism in Individuals Without Diabetes: The Whitehall II Cohort Study

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OBJECTIVE

Autonomic nervous system dysfunction is associated with impaired glucose metabolism, but the temporality of this association remains unclear in individuals without diabetes. We investigated the association of autonomic function with 5-year changes in glucose metabolism in individuals without diabetes.

RESEARCH DESIGN AND METHODS

Analyses were based on 9,000 person-examinations for 3,631 participants without diabetes in the Whitehall II cohort. Measures of autonomic function included 5-min resting heart rate and six heart rate variability (HRV) indices. Associations between baseline autonomic function measures and 5-year changes in fasting and 2-h plasma glucose, serum insulin concentrations, insulin sensitivity (insulin sensitivity index [$ISI_{0–120}$] and HOMA of insulin sensitivity), and β-cell function (HOMA of β-cell function) were estimated in models adjusting for age, sex, ethnicity, metabolic factors, and medication.

RESULTS

A 10-bpm higher resting heart rate was associated with 5-year changes in fasting and 2-h insulin and $ISI_{0–120}$ of 3.3% change (95% CI 1.8; 4.8), $P < 0.001$; 3.3% change (1.3; 5.3), $P = 0.001$; and −1.4% change (−2.4; −0.3), $P = 0.009$, respectively. In models adjusted for age, sex, and ethnicity, higher baseline values of several HRV indices were associated with a 5-year decrease in fasting and 2-h insulin and $ISI_{0–120}$. However, significance was lost by full adjustment. A majority of HRV indices exhibited a trend toward higher values being associated with lower insulin levels and higher insulin sensitivity.

CONCLUSIONS

Higher resting heart rate in individuals without diabetes is associated with future unfavorable changes in insulin levels and insulin sensitivity. Associations may be mediated via autonomic function; however, results are inconclusive. Resting heart rate may be a risk marker for future pathophysiological changes in glucose metabolism.

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People with diabetes have a higher prevalence of autonomic dysfunction. The prevalence of cardiovascular autonomic neuropathy (CAN) ranges from 20% in the general population with diabetes (1,2) to 65% in people with long-standing diabetes (3). In addition to established cardiometabolic risk factors, CAN is an independent determinant of cardiovascular morbidity, progression of diabetic nephropathy, and overall mortality (4–6). Autonomic imbalance has been associated with reduced insulin sensitivity and β-cell function in individuals with recent onset of type 1 and type 2 diabetes and has been suggested to be mediated by changes in the innervation of the endocrine pancreas (7) where pancreatic islets are innervated by both parasympathetic and sympathetic nerves and are involved in pancreatic hormone secretion (8). In addition, peripheral insulin sensitivity may be associated with autonomic function, as hyperinsulinemic-euglycemic clamp studies have demonstrated that insulin sensitivity can be affected by autonomic blockade in obese insulin-resistant individuals (9). In concert, autonomic dysfunction may affect both β-cell function and insulin resistance.

Autonomic imbalance has been observed in individuals with prediabetes (10) and the metabolic syndrome (11,12) and is associated with incident diabetes (13,14), suggesting that alterations in autonomic function may contribute to the pathogenesis of diabetes. Similar associations have been found in the offspring of patients with type 2 diabetes (15), implying that a pathological interplay between autonomic neuropathy and glucose metabolism exists not only in diabetes but also in individuals with increased risk of the disease. Indeed, some cross-sectional cohort studies have shown that CAN assessed by heart rate variability (HRV) is associated with lower insulin sensitivity in individuals without diabetes (16,17). Furthermore, observational data suggest that autonomic function may be affected prior to development of hyperglycemia. This indicates that autonomic dysfunction may precede glycemic dysfunction. Thus, substantial evidence links autonomic dysfunction with impaired glucose metabolism. However, as the above-mentioned findings are based on cross-sectional studies, large prospective studies are needed to elucidate whether autonomic dysfunction precedes glycemic dysfunction in individuals without diabetes.

We hypothesize that autonomic dysfunction in individuals without diabetes precedes future changes in glucose metabolism that may lead to diabetes.

In this cohort study with repeated measurements of glucose metabolism, we aimed to investigate the prospective associations of measures of cardiac autonomic status as a proxy for autonomic function with subsequent 5-year changes in fasting and 2-h plasma glucose and serum insulin concentrations, insulin sensitivity, and β-cell function in individuals without diabetes.

RESEARCH DESIGN AND METHODS

Study Participants

Study participants are from the Whitehall II study, an occupational cohort of 10,308 British civil servants (6,896 men and 3,412 women aged 35–55 years) of mainly white ethnicity recruited between 1985 and 1988 (phase 1) (18). The cohort has been followed at eight subsequent phases, ~2.5 years apart. All study phases included a questionnaire, and every second phase (5 years apart) also included a clinical health examination (phases 1, 3, 5, 7, and 9). Phase 5 (1997–1999) was the first phase where resting heart rate and HRV were measured and therefore was the baseline for the current analyses. A total of 7,870 participated at phase 5, 6,967 at phase 7 (2002–2004), and 6,761 at phase 9 (2007–2009).

At phases 5, 7, and 9, a standard 2-h 75-g oral glucose tolerance test (OGTT) was performed in the morning after an overnight fast (≥8 h of fasting). For approximately one-third of the examinations, the OGTT was administered in the afternoon after a light fat-free breakfast (≥5 h of fasting), and data from these examinations were not included in the analysis. Diabetes was diagnosed by the treating physician (outside the study) or during screening ascertained throughout follow-up by OGTTs administered every 5 years with diabetes defined according to the World Health Organization (19). Prediabetes was defined by fasting glucose between or equal to 6.1 and 7.0 mmol/L and/or a 2-h glucose level between or equal to 7.8 and 11.1 mmol/L. Diabetes was defined by measures above these levels.

Autonomic function was assessed in a subset of the participants: in 54% at phase 5, 64% at phase 7, and 83% at phase 9.

During follow-up, participants were censored if they died, were lost to follow-up, were diagnosed with diabetes, or developed heart disease, such as ischemic heart disease and arrhythmias, diagnosed either at study examination or ascertained by register-based follow-up. We excluded 7,183 (35.8%) person-examinations for which the participant had been fasting <8 h (where OGTTs had been administered in the afternoon or the participant was known to have diabetes) and another 951 person-examinations because the participants had developed heart disease. Up to a total of 9,000 person-examinations for 3,631 participants without known diabetes, ischemic heart disease, or arrhythmias were analyzed (5,709 person-examinations for 2,519 participants for the analyses of HRV).

The U.K. NHS Health Research Authority London-Harrow Ethics Committee reviewed and approved the study. Written informed consent was obtained from each participant at each examination phase. The study was conducted according to the principles of the Declaration of Helsinki.

Measurements

Plasma glucose (fasting and 120 min), serum insulin (fasting and 120 min), HbA_{1c}, serum lipids, and blood pressure at phases 5, 7, and 9 were measured as previously described (20,21). Whole-body insulin sensitivity was estimated by the insulin sensitivity index (ISI_{0-120}) based on fasting and 2-h values of glucose and insulin as well as body weight (22). Insulin sensitivity in the fasting state was assessed based on fasting plasma glucose and serum insulin concentrations using HOMA of insulin sensitivity (HOMA-IS) (23). β-Cell function was estimated based on fasting plasma glucose and serum insulin concentrations using HOMA of β-cell function (HOMA-β) (23).

HRV indices characterizing autonomic status were derived from 5-min resting 12-lead ECG recordings obtained subsequent to 5 min of rest in the supine position at phases 5 and 7. Recordings were filtered through an automated algorithm, allowing the analyses of suitable normal-to-normal sinus rhythm R-R intervals without the presence of arrhythmias, ectopic beats, and branch blocks (N-N intervals). Indices of HRV were

analyzed both in the time domain, the SD of all N-N intervals (SDNN) and the root mean square of the sum of the squares of differences between consecutive N-N intervals (RMSSD), and in the frequency domain, by using a Blackman-Tukey algorithm: low-frequency (LF) power (in the 0.04–0.15 Hz frequency band), high-frequency (HF) power (in the 0.15–0.4 Hz frequency band), and total power (in the ≤0.4 Hz frequency band). The ratio between LF and HF power (LF-to-HF ratio) was calculated. Resting heart rate (rHR) was calculated from the ECG recordings. RMSSD and HF power outcomes are associated mainly with parasympathetic modulations, whereas the remaining measures characterize mixed sympathetic and parasympathetic influences.

Information on smoking habits (never/former/current), physical activity (hours per week of mild, moderate, and vigorous physical activity), and medication use was collected using self-administered questionnaires at phases 5, 7, and 9 (24).

Statistical Analysis

In the main analysis, the following glycemic outcomes were studied: fasting and 2-h serum insulin, fasting and 2-h plasma glucose, HOMA-IS and $ISI_{0–120}$, HOMA-β, and HbA_{1c}. Outcomes with a skewed distribution (fasting and 2-h serum insulin, HOMA-IS, $ISI_{0–120}$, and HOMA-β) were log transformed before analysis in order to fulfill the assumption of normally distributed model residuals. Heart rate and the six HRV indices (SDNN, RMSSD, HF power, LF power, LF-to-HF ratio, and total power) were included as exposures. All exposures except heart rate were $\log_2$ transformed prior to analysis.

In the analyses of the six HRV indices, the subset of participants with autonomic function assessed was used. For the analysis of heart rate, the total study population was included. HbA_{1c} was only measured at phases 7 and 9, so for this outcome, phase 5 was not used. For most of the covariates, <5% of the values were missing but up to 9% of the values were missing for physical activity. To avoid exclusion of patients with missing values, missing data on the covariates at each phase were imputed by using the multivariate imputations by chained equations method (25) with missing-at-random assumptions (25 imputations) and including a number of auxiliary data on the participants not used in the analyses. Estimates of parameters of interest were averaged across the imputation copies according to Rubin's rules (26).

In each 5-year observation window of two consecutive phases, we studied the associations of baseline levels of heart rate and HRV indices and follow-up levels of the different outcomes, adjusting for baseline level of the outcome. Because the same individual may contribute with up to three observations to the analyses, associations were estimated using linear mixed-effects models with a participant-specific random intercept and slope to account for the correlation of repeated measurements within participants.

All analyses were adjusted for age, sex, ethnicity, and baseline value of the outcome studied (model 1). HRV indices were further adjusted for the simultaneously measured heart rate. Additional adjustments included BMI, physical activity, smoking, systolic blood pressure, total cholesterol, triglycerides, tricyclic antidepressants, diuretics, and β-blockers (model 2). In model 1, we tested for a modifying effect of baseline glycemic state (normal glucose tolerance or prediabetes) on the association with heart rate and HRV indices. Glycemic state was treated as a time-varying confounder, which allowed the same participant to contribute with person-examinations first to the normal glucose tolerance group and later to the prediabetes group (and vice versa).

To allow direct comparisons of effect sizes between the exposure variables, we further calculated standardized regression coefficients for the subset of the population for whom heart rate and all six HRV indices were available at the same time points, i.e., the subset with autonomic function assessed. HRV indices were log transformed before standardization, and the adjustments used in model 2 were applied.

Statistical analyses were performed in R, version 3.3.3 (The R Foundation for Statistical Computing), and SAS, version 9.4 (SAS Institute, Cary, NC).

RESULTS

Median (25th; 75th percentile) time between phases 5, 7, and 9 was 5.1 years (5.0; 5.5). All measures of HRV diminished during the study period. Characteristics of the study population by study phase are shown in Table 1.

We found no statistically significant modifying effect of prediabetes status for any associations $P \geq 0.051$, so associations were estimated for normal glucose tolerance and prediabetes combined.

Associations of Heart Rate and HRV Indices With 5-Year Changes in Serum Insulin Concentrations

Higher resting heart rate was significantly associated with a 5-year increase in levels of fasting serum insulin in all statistical models. Higher values of total power were associated with a reduction in fasting serum insulin levels 5 years after baseline in model 1, but associations lost significance after further adjustment. Similar trends for the HRV indices SDNN, RMSSD, and total power were seen (Table 2).

Overall, heart rate and HRV indices showed a direction of associations with 2-h insulin that was similar to that for fasting insulin. A higher baseline heart rate was associated with a 5-year increase in 2-h insulin in both models. LF power and total power were associated with a 5-year drop in 2-h serum insulin in model 1; however, significance was lost in model 2. Similar trends for the HRV indices SDNN and HF power were identified (Table 2 and Fig. 1).

Associations Between Heart Rate and HRV Indices and 5-Year Changes in Insulin Sensitivity

In model 1, higher heart rate was significantly associated with a decrease in insulin sensitivity assessed by $ISI_{0–120}$ 5 years after baseline. Higher levels of SDNN, LF power, and total power were significantly associated with higher insulin sensitivity. After full adjustment, only heart rate remained significantly associated with $ISI_{0–120}$. The trends toward higher SDNN and LF power being associated with higher insulin sensitivity were seen only in model 1 (Table 2 and Fig. 1).

When insulin sensitivity was assessed by HOMA-IS, similar associations were seen but of smaller magnitude and only significant for heart rate (Supplementary Table 1 and Supplementary Fig. 1).

Associations Between Heart Rate and HRV Indices and 5-Year Changes in β-Cell Function

Higher baseline heart rate was associated with a 5-year increase in HOMA-β in all models. The opposite associations were seen for HF power, but the associations lost statistical significance in model

Table 1—Characteristics of the study population at each study phase

	Phase 5	Phase 7	Phase 9
N	4,271	4,294	3,343
Men, % (95% CI)	70.7 (69.3; 72.0)	72.0 (70.6; 73.3)	71.7 (70.2; 73.3)
Caucasian, % (95% CI)	92.0 (91.1; 92.8)	92.6 (91.8; 93.4)	93.0 (92.1; 93.9)
Age (years)	55.0 (5.9)	60.4 (5.8)	65.1 (5.8)
Height (cm)	172.2 (9.1)	171.4 (9.1)	171.3 (9.1)
BMI (kg/m^2)	26.1 (3.9)	26.6 (4.3)	26.5 (4.3)
Waist circumference (cm)	90.5 (11.6)	93.2 (12.0)	94.0 (11.8)
Current smoker (%)	10.6 (9.7; 11.5)	8.6 (7.8; 9.5)	5.8 (5.0; 6.6)
Moderate-to-vigorous exercise (h/week)	11.3 (4.5; 19.8)	11.8 (4.5; 20.3)	—
Alcohol intake (units/week)	10.0 (3.0; 20.0)	9.0 (3.0; 18.0)	7.0 (2.0; 16.0)
Systolic blood pressure (mmHg)	122.2 (16.3)	127.8 (16.7)	125.4 (15.8)
Diastolic blood pressure (mmHg)	77.3 (10.5)	74.6 (10.5)	71.7 (10.0)
Medication, % (95% CI)			
Tricyclic antidepressants	2.2 (1.8; 2.7)	2.6 (2.1; 3.1)	3.4 (2.8; 4.0)
Diuretics	2.9 (2.4; 3.5)	7.4 (6.6; 8.2)	11.2 (10.1; 12.3)
β-Blockers	4.6 (4.0; 5.3)	7.9 (7.1; 8.7)	6.5 (5.7; 7.4)
Blood measurements			
Fasting plasma glucose (mmol/L)	5.1 (0.7)	5.3 (0.7)	5.2 (0.6)
2-h plasma glucose (mmol/L)	5.8 (1.7)	6.3 (1.9)	6.4 (1.9)
HbA_{1c} (mmol/mol)	—	38.0 (5.4)	38.0 (4.9)
HbA_{1c} (%)	—	5.6 (0.5)	5.6 (0.4)
Fasting serum insulin (pmol/L)	7.0 (4.9; 10.1)	7.0 (4.7; 10.6)	6.5 (4.3; 10.1)
2-h serum insulin (pmol/L)	32.6 (19.8; 53.2)	37.8 (23.4; 63.6)	41.0 (25.2; 68.7)
$ISI_{0–120}$	38.1 (29.7; 49.0)	34.4 (26.4; 44.4)	33.8 (25.7; 43.9)
HOMA-IS	1.6 (1.1; 2.4)	1.6 (1.1; 2.6)	1.5 (1.0; 2.4)
HOMA-β	92.1 (65.2; 131.4)	80.0 (55.3; 118.9)	81.5 (55.4; 120.0)
Total cholesterol (mmol/L)	5.9 (1.1)	5.8 (1.0)	5.4 (1.0)
HDL cholesterol (mmol/L)	1.5 (0.4)	1.6 (0.4)	1.6 (0.4)
LDL cholesterol (mmol/L)	3.9 (0.9)	3.6 (0.9)	3.2 (1.0)
Triglycerides (mmol/L)	1.3 (0.9)	1.3 (0.9)	1.2 (0.7)
Heart rate measurements			
rHR from ECG (bpm)	67.2 (11.1)	67.8 (11.6)	65.5 (11.1)
SDNN (ms)	34.6 (26.3; 44.8)	33.8 (25.6; 44.9)	30.4 (22.6; 41.3)
RMSSD (ms)	20.5 (13.9; 29.5)	20.2 (13.5; 30.2)	18.0 (12.3; 26.6)
LF power (ms^2)	315.8 (170.0; 572.8)	286.4 (160.0; 518.0)	234.7 (121.4; 468.1)
HF power (ms^2)	132.2 (63.1; 262.5)	116.0 (55.5; 234.1)	92.1 (45.2; 189.8)
LF-to-HF ratio	2.56 (1.52; 4.04)	2.62 (1.59; 4.06)	2.69 (1.59; 4.14)
Total power (ms^2)	1,068 (619; 1,795)	1,010 (577; 1,778)	815 (453; 1,513)

Data are means (SD) or median (25th; 75th percentiles) unless otherwise indicated. *N*, number of participants.

2 (Supplementary Table 1 and Supplementary Fig. 1).

Associations Between Heart Rate and HRV Indices and Changes in Glycemic Measures

Higher heart rate was significantly associated with very small increases in fasting and 2-h glucose and HbA_{1c} levels in model 1 but lost significance in model 2. Higher LF-to-HF ratio was associated with small decreases in 2-h fasting glucose levels in both model 1 and model 2 (Fig. 1 and Supplementary Table 2).

Effect Size

In comparison of the standardized regression coefficients, heart rate was overall more strongly associated with the outcomes compared with HRV indices. However, all effect sizes were relatively small (Fig. 1).

CONCLUSIONS

The current study investigated the temporal associations of resting heart rate and HRV with 5-year changes in glucose metabolism in a large population of individuals without diabetes. Our results show that higher resting heart rate was associated with subsequent increases in fasting insulin, 2-h insulin, and β-cell function and with a decrease in insulin sensitivity but was not associated with glycemia in a clinically significant manner. Few HRV indices reflecting both parasympathetic modulations and a mixture of sympathetic and parasympathetic modulations were significantly associated with insulin measures but only in models adjusted for age, sex, and ethnicity. More favorable baseline values of these HRV indices were associated with decreases in fasting insulin, 2-h insulin, β-cell function, and insulin sensitivity. Similar trends toward the same associations were seen for the majority of all HRV outcomes in the fully adjusted models; however, only few estimates had *P* values close to 0.05. No associations of HRV measures with HbA_{1c}, fasting glucose, or 2-h glucose were observed in the fully adjusted models.

Table 2—Effect sizes (95% CI) of baseline heart rate or HRV on 5-year changes in serum insulin concentrations and insulin sensitivity

	Model	Fasting serum insulin (% diff.)				2-h serum insulin (% diff.)				ISI_{0-120} (% diff.)			
		N	Npe	Estimate	*P*	*N*	Npe	Estimate	*P*	*N*	Npe	Estimate	*P*
rHR (10 bpm)	1	3,631	9,000	3.4 (2.0; 4.8)	<0.001	3,631	9,000	4.0 (2.2; 5.9)	<0.001	3,631	9,000	−2.0 (−2.9; −1.0)	<0.001
	2	3,631	9,000	3.3 (1.8; 4.8)	<0.001	3,631	9,000	3.3 (1.3; 5.3)	0.001	3,631	9,000	−1.4 (−2.4; −0.3)	0.009
SDNN (doubling)	1	2,519	5,709	−2.4 (−5.2; 0.4)	0.089	2,519	5,709	−5.1 (−9.1; −1.0)	0.016	2,519	5,709	3.1 (0.7; 5.5)	0.010
	2	2,519	5,709	−0.5 (−3.3; 2.3)	0.726	2,519	5,709	−3.1 (−7.1; 1.1)	0.146	2,519	5,709	1.8 (−0.5; 4.1)	0.134
RMSSD (doubling)	1	2,519	5,709	−1.4 (−3.5; 0.7)	0.177	2,519	5,709	−2.3 (−5.2; 0.7)	0.134	2,519	5,709	0.9 (−0.8; 2.6)	0.304
	2	2,519	5,709	−0.5 (−2.5; 1.6)	0.643	2,519	5,709	−1.0 (−4.0; 2.0)	0.504	2,519	5,709	0.1 (−1.6; 1.7)	0.932
LF power (doubling)	1	2,519	5,709	−1.2 (−2.4; 0.1)	0.069	2,519	5,709	−2.1 (−3.9; −0.2)	0.027	2,519	5,709	1.4 (0.4; 2.4)	0.008
	2	2,519	5,709	−0.1 (−1.4; 1.1)	0.822	2,519	5,709	−1.1 (−2.9; 0.8)	0.256	2,519	5,709	0.7 (−0.3; 1.7)	0.156
HF power (doubling)	1	2,519	5,709	−1.1 (−2.2; 0.0)	0.046	2,519	5,709	−1.4 (−3.0; 0.1)	0.073	2,519	5,709	0.7 (−0.1; 1.6)	0.102
	2	2,519	5,709	−0.3 (−1.3; 0.8)	0.601	2,519	5,709	−0.5 (−2.1; 1.1)	0.521	2,519	5,709	0.1 (−0.7; 1.0)	0.743
LF-to-HF ratio (doubling)	1	2,519	5,709	0.5 (−1.1; 2.2)	0.556	2,519	5,709	−0.5 (−2.8; 2.0)	0.699	2,519	5,709	0.8 (−0.5; 2.0)	0.246
	2	2,519	5,709	0.4 (−1.2; 2.0)	0.620	2,519	5,709	−0.7 (−3.1; 1.6)	0.537	2,519	5,709	1.0 (−0.3; 2.2)	0.140
Total power (doubling)	1	2,519	5,709	−1.3 (−2.7; 0.2)	0.080	2,519	5,709	−2.5 (−4.6; −0.4)	0.018	2,519	5,709	1.6 (0.4; 2.7)	0.008
	2	2,519	5,709	−0.2 (−1.6; 1.2)	0.745	2,519	5,709	−1.5 (−3.6; 0.6)	0.167	2,519	5,709	0.9 (−0.2; 2.1)	0.117

Model 1, adjusted for age, sex, ethnicity, study phase, and baseline value of the outcome studied. For HRV indices, further adjustment for heart rate obtained as part of the HRV analyses. Model 2, further adjustment for BMI, physical activity, smoking, systolic blood pressure, total cholesterol, triglycerides, tricyclic antidepressants, diuretics, and β-blockers. diff., difference; *N*, number of participants used in the particular analysis; Npe, number of person-examinations used in the particular analysis; *P*, *P* value for the test of the effect being equal to zero.

Insulin

Our results show that higher and less favorable levels of resting heart rate were associated with future increases in both fasting and 2-h insulin levels. These associations may in part be mediated through autonomic function, as higher and favorable levels HRV in heart rate–adjusted analyses in several cases seemed to trend toward an association with higher future levels of insulin in the fasting state and during glucose administration. It is known that insulin itself can influence the autonomic nervous system (27) by reducing parasympathetic function and potentiating sympathetic drive. This insulin-induced change in autonomic tone is, however, attenuated in insulin-resistant individuals (28), suggesting that alterations in autonomic tone in insulin-resistant individuals are due to pathological mechanisms less closely related to hyperinsulinemia. As the endocrine pancreas is innervated by the autonomic nervous system (8), it is plausible that autonomic dysfunction may elicit future dysinsulinemia by an imbalance in nervous control of the pancreatic islet. However, owing to the paucity of significant associations between HRV indices and insulin measures, it cannot be concluded that autonomic function is associated with insulin levels in individuals without diabetes. These finding are novel, as no studies to our knowledge have previously addressed the temporal relationship of resting heart rate and HRV with future changes in insulin levels in individuals without diabetes.

Insulin Sensitivity

Higher heart rate was associated with lower future whole-body insulin sensitivity in all models. As for insulin, higher and more favorable levels of several HRV indices were associated with increased insulin sensitivity. However, only trends of this association remained after full adjustment. Similar but less significant associations were found when insulin sensitivity was assessed by HOMA-IS. Cross-sectional studies have reported autonomic imbalance to be associated with insulin resistance in obese individuals (29). Also, intervention studies demonstrating improvements in insulin sensitivity by weight loss, training, or ACE inhibition have shown improvements in parasympathetic activity (28,30,31). In

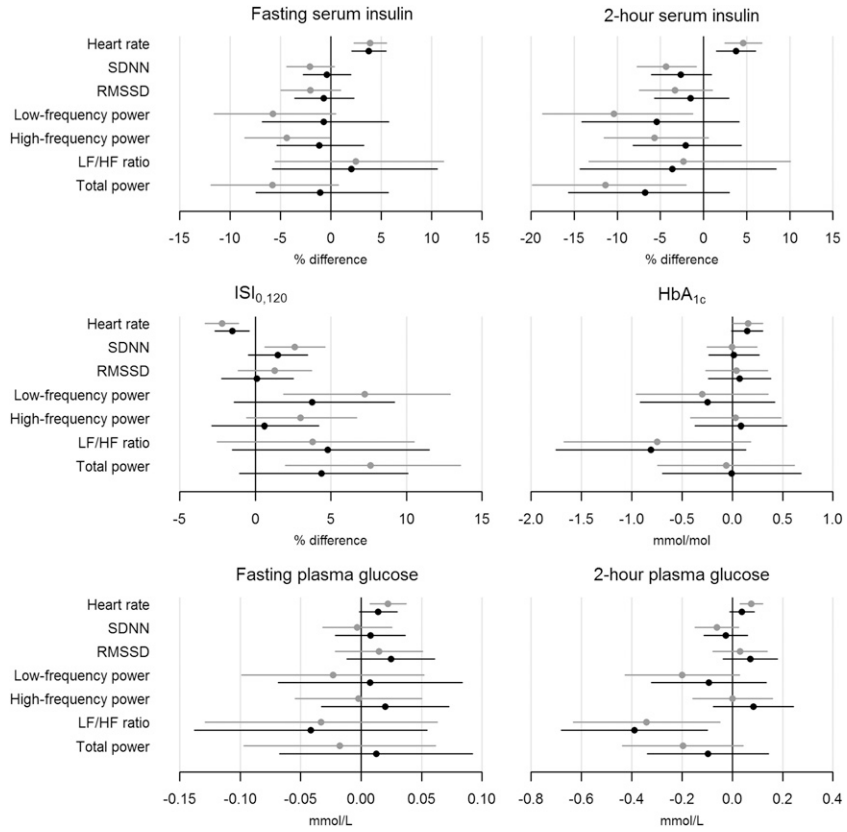

Figure 1—Effect (with 95% CI) of one population SD difference in heart rate or in the log of HRV indices at baseline on subsequent 5-year changes in markers of glucose regulation. The associations are adjusted for age, sex, ethnicity, study phase, and baseline value of the outcome studied (gray) with further adjustment for BMI, physical activity, smoking, systolic blood pressure, total cholesterol, triglycerides, tricyclic antidepressants, diuretics, and β-blockers (black). For HRV indices, further adjustment for heart rate was obtained as part of the HRV analyses.

concert with the above-mentioned studies, our results may indicate that higher heart rate and autonomic dysfunction could be associated with future loss of insulin sensitivity. However, only heart rate remained significantly associated with future changes in insulin sensitivity in fully adjusted models, which could imply that pathways other than autonomic dysfunction may mediate the associations or that heart rate is just a risk marker of other pathogenic mechanisms as stated above. These findings are novel, as no studies to our knowledge have previously addressed the temporal relationship of resting heart rate and HRV with future changes in insulin sensitivity in individuals without diabetes.

β-Cell Function

Our findings suggest that less favorable (higher) levels of heart rate are associated with improved future β-cell function. This seems to contradict our finding with respect to levels of insulin and insulin sensitivity, where more favorable measures of heart rate were associated with improvements in glucose control. It is possible that these changes are a result of a compensatory improvement in β-cell function in nondiabetic states. However, it is more likely that our association between heart rate and β-cell function may be a spurious finding and an artifact caused by improvements in insulin sensitivity and unaffected measures of glycemia. Low peripheral insulin sensitivity is associated with increased secretion of insulin (32,33). If insulin sensitivity is improved and glucose levels remain stable, this would lead to reduced levels of insulin and a false reduction in β-cell function as estimated by the HOMA-β equation.

Glycemia

No clinically meaningful associations of resting heart rate or HRV indices with measures of glycemia were observed. Fasting glucose levels are mainly determined by hepatic glucose production, whereas increased 2-h glucose concentrations mainly reflect peripheral glucose uptake (34). The autonomic nervous system is associated with both systems, innervating the liver (35,36), affecting hepatic glucose production and release (37), and possibly regulating muscle glucose uptake in a non-insulin-dependent manner (37,38). It is possible that we did not find any association between heart rate and HRV-based indices of autonomic dysfunction and glycemic measures owing to compensatory mechanisms in this cohort of adults without diabetes enabling preserved glucose homeostasis. This compensation could be mediated through, for example, increased insulin levels, as seen in our results discussed above.

Strengths and Limitations

Our study benefits from its large sample size, the comprehensive measurements of outcomes and exposures assessed simultaneously, and the extensive adjustment for confounders. Importantly, the prospective design allowed us to assess the temporal association between heart rate and HRV and changes in glucose metabolism, whereas associations in previous cross-sectional studies may be attributable to reverse causality.

Resting heart rate is not a gold standard measure of autonomic function, as it may be affected by several factors such as physical fitness, hemoglobin levels, and inflammation. Therefore, any conclusions about the associations of heart rate and autonomic function should be drawn with caution. Also, the study holds no pure sympathetic measures. The lack of associations between autonomic function measures and glucose metabolism may be due to this limitation, as sympathetic activation is associated with insulin secretion. Further limitations include the observational design that precludes causal inferences. However, the current study provides evidence for temporal associations.

$ISI_{0–120}$ and HOMA-IS correlate only moderately well with the euglycemic-hyperinsulinemic clamp (39). Thus, our assessment of insulin sensitivity was less precise than the gold standard. In addition, our study did not include dynamic assessments of β-cell function; thus, we could not examine β-cell function relative to insulin sensitivity using the disposition index. The association between

autonomic function and glucose regulation may have been underestimated owing to censoring of study participants with comorbidities in whom the associations may have been more pronounced. The associations found between heart rate and insulin levels and insulin sensitivity may be due to residual confounding not addressed in the current study such as inflammation and physical fitness.

The study population was predominantly of European descent, so the results may not be generalized to other ethnic groups. Also, the cohort is based on people employed as civil servants at the study start, excluding, for example, unemployed people and people employed in the private sector. The study may therefore not be fully generalizable to the general population.

Conclusion

In summary, our study demonstrates that more favorable baseline levels of heart rate and autonomic function assessed by HRV indices were associated with improvements in insulin sensitivity and lower serum insulin concentrations in individuals without diabetes. Associations were found for both parasympathetic and mixed sympathetic and parasympathetic measures. However, only trends of these association were found for HRV indices in fully adjusted models, implying that association between heart rate and future changes in glucose metabolism may be mediated via mechanisms other than autonomic dysfunction or that heart rate is merely a risk marker of other pathological mechanisms. Effect sizes were moderate, but on a population level these results may suggest that elevated heart rate marks subsequent deterioration of glucose metabolism. No corresponding associations were observed for HbA_{1c} or fasting or 2-h plasma glucose.

We find that these indicate that resting heart rate is a potential risk marker for future deteriorating of glucose metabolism in individuals without diabetes. Notably, these future changes are seen for fasting and 2-h insulin and insulin sensitivity, which have not been investigated previously. These findings suggest that heart rate is associated with the underlying pathophysiology leading to diabetes and support the few studies showing heart rate to be associated with future development of dysglycemia (40) and diabetes (13).

Prospective studies following individuals from nondiabetic states to overt diabetes are needed to elucidate whether autonomic dysfunction is indeed associated with adverse changes in glucose metabolism leading to the disease.

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Data Availability. Whitehall II data, protocols, and other metadata are available to bona fide researchers for research purposes. Please refer to the Whitehall II data sharing policy at http://www.ucl.ac.uk/whitehallII/data-sharing.

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References

1. Valensi P, Pariès J, Attali JR; French Group for Research and Study of Diabetic Neuropathy. Cardiac autonomic neuropathy in diabetic patients: influence of diabetes duration, obesity, and microangiopathic complications–the French multicenter study. Metabolism 2003;52:815–820
2. Ziegler D, Dannehl K, Mühlen H, Spüler M, Gries FA. Prevalence of cardiovascular autonomic dysfunction assessed by spectral analysis, vector analysis, and standard tests of heart rate variation and blood pressure responses at various stages of diabetic neuropathy. Diabet Med 1992;9:806–814
3. Low PA, Benrud-Larson LM, Sletten DM, et al. Autonomic symptoms and diabetic neuropathy: a population-based study. Diabetes Care 2004;27:2942–2947
4. Tesfaye S, Boulton AJ, Dyck PJ, et al.; Toronto Diabetic Neuropathy Expert Group. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care 2010;33:2285–2293
5. Wheeler SG, Ahroni JH, Boyko EJ. Prospective study of autonomic neuropathy as a predictor of mortality in patients with diabetes. Diabetes Res Clin Pract 2002;58:131–138
6. Ziegler D, Zentai CP, Perz S, et al.; KORA Study Group. Prediction of mortality using measures of cardiac autonomic dysfunction in the diabetic and nondiabetic population: the MONICA/KORA Augsburg Cohort study. Diabetes Care 2008;31:556–561
7. Ziegler D, Strom A, Bönhof G, et al.; GDS Group. Differential associations of lower cardiac vagal tone with insulin resistance and insulin secretion in recently diagnosed type 1 and type 2 diabetes. Metabolism 2018;79:1–9
8. Thorens B. Neural regulation of pancreatic islet cell mass and function. Diabetes Obes Metab 2014;16(Suppl. 1):87–95
9. Gamboa A, Okamoto LE, Arnold AC, et al. Autonomic blockade improves insulin sensitivity in obese subjects. Hypertension 2014;64:867–874
10. Papanas N, Vinik AI, Ziegler D. Neuropathy in prediabetes: does the clock start ticking early? Nat Rev Endocrinol 2011;7:682–690
11. Assoumou HG, Pichot V, Barthelemy JC, et al. Metabolic syndrome and short-term and long-term heart rate variability in elderly free of clinical cardiovascular disease: the PROOF study. Rejuvenation Res 2010;13:653–663
12. Stein PK, Barzilay JI, Domitrovich PP, et al. The relationship of heart rate and heart rate variability to non-diabetic fasting glucose levels and the metabolic syndrome: the Cardiovascular Health Study. Diabet Med 2007;24:855–863
13. Carnethon MR, Golden SH, Folsom AR, Haskell W, Liao D. Prospective investigation of autonomic nervous system function and the development of type 2 diabetes: the Atherosclerosis Risk in Communities study, 1987-1998. Circulation 2003;107:2190–2195
14. Wulsin LR, Horn PS, Perry JL, Massaro JM, D'Agostino RB. Autonomic imbalance as a predictor of metabolic risks, cardiovascular disease, diabetes, and mortality. J Clin Endocrinol Metab 2015;100:2443–2448
15. Svensson MK, Lindmark S, Wiklund U, et al. Alterations in heart rate variability during everyday life are linked to insulin resistance. A role of dominating sympathetic over parasympathetic nerve activity? Cardiovasc Diabetol 2016;15:91
16. Hillebrand S, Swenne CA, Gast KB, et al. The role of insulin resistance in the association between body fat and autonomic function. Nutr Metab Cardiovasc Dis 2015;25:93–99
17. Saito I, Hitsumoto S, Maruyama K, et al. Heart rate variability, insulin resistance, and insulin sensitivity in Japanese adults: the Toon Health Study. J Epidemiol 2015;25:583–591

18. Marmot M, Brunner E. Cohort profile: the Whitehall II study. Int J Epidemiol 2005;34:251–256
19. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539–553
20. Tabák AG, Jokela M, Akbaraly TN, Brunner EJ, Kivimäki M, Witte DR. Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. Lancet 2009;373:2215–2221
21. Færch K, Witte DR, Tabák AG, et al. Trajectories of cardiometabolic risk factors before diagnosis of three subtypes of type 2 diabetes: a post-hoc analysis of the longitudinal Whitehall II cohort study. Lancet Diabetes Endocrinol 2013;1:43–51
22. Gutt M, Davis CL, Spitzer SB, et al. Validation of the insulin sensitivity index (ISI(0,120)): comparison with other measures. Diabetes Res Clin Pract 2000;47:177–184
23. Herder C, Færch K, Carstensen-Kirberg M, et al. Biomarkers of subclinical inflammation and increases in glycaemia, insulin resistance and beta-cell function in non-diabetic individuals: the Whitehall II study. Eur J Endocrinol 2016;175:367–377
24. Stringhini S, Batty GD, Bovet P, et al. Association of lifecourse socioeconomic status with chronic inflammation and type 2 diabetes risk: the Whitehall II prospective cohort study. PLoS Med 2013;10:e1001479
25. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res 2007;16:219–242
26. Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. BMC Med Res Methodol 2009;9:57
27. Manzella D, Paolisso G. Cardiac autonomic activity and type II diabetes mellitus. Clin Sci (Lond) 2005;108:93–99
28. Bergholm R, Westerbacka J, Vehkavaara S, Seppälä-Lindroos A, Goto T, Yki-Järvinen H. Insulin sensitivity regulates autonomic control of heart rate variation independent of body weight in normal subjects. J Clin Endocrinol Metab 2001;86:1403–1409
29. Straznicky NE, Lambert EA, Grima MT, et al. The effects of dietary weight loss on indices of norepinephrine turnover: modulatory influence of hyperinsulinemia. Obesity (Silver Spring) 2014;22:652–662
30. Goulopoulou S, Baynard T, Franklin RM, et al. Exercise training improves cardiovascular autonomic modulation in response to glucose ingestion in obese adults with and without type 2 diabetes mellitus. Metabolism 2010;59:901–910
31. Voulgari C, Pagoni S, Vinik A, Poirier P. Exercise improves cardiac autonomic function in obesity and diabetes. Metabolism 2013;62:609–621
32. Bergman RN, Phillips LS, Cobelli C. Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. J Clin Invest 1981;68:1456–1467
33. Larsson H, Ahrén B. Failure to adequately adapt reduced insulin sensitivity with increased insulin secretion in women with impaired glucose tolerance. Diabetologia 1996;39:1099–1107
34. Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of β-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. Diabetes Care 2006;29:1130–1139
35. Kalsbeek A, Bruinstroop E, Yi CX, Klieverik L, Liu J, Fliers E. Hormonal control of metabolism by the hypothalamus-autonomic nervous system-liver axis. Front Horm Res 2014;42:1–28
36. Yi CX, la Fleur SE, Fliers E, Kalsbeek A. The role of the autonomic nervous liver innervation in the control of energy metabolism. Biochim Biophys Acta 2010;1802:416–431
37. Seoane-Collazo P, Fernø J, Gonzalez F, et al. Hypothalamic-autonomic control of energy homeostasis. Endocrine 2015;50:276–291
38. Nonogaki K. New insights into sympathetic regulation of glucose and fat metabolism. Diabetologia 2000;43:533–549
39. Simonson DC. Surrogate measures of insulin resistance: does one size fit all? Diabetologia 2015;58:207–210
40. Wang L, Cui L, Wang Y, et al. Resting heart rate and the risk of developing impaired fasting glucose and diabetes: the Kailuan prospective study. Int J Epidemiol 2015;44:689–699